REMARKS

Reconsideration and allowance are respectfully requested.

Claims 18 to 21 have been canceled. New claims 22 to 24 have been added. The new claims are fully supported by the specification and claims as originally filed. No new matter has been added by the amendments to the claims.

The only rejections remaining in the application are under 35 U.S.C. § 103(a)

The Rejections Under 35 U.S.C. § 103(a)

Claims 18 to 21 have been canceled, and so the rejection of these claims as obvious is moot.

To the extent the Examiner might consider extending the same grounds for rejection to claims 22 to 24, applicants respectfully traverse, and request reconsideration.

Claims 22 to 24 all include the limitation that the PEGylation must be a branched, 40 kDa PEG group. An example of such a molecule is specifically disclosed in the specification (see, e.g., Example 5, page 22, lines 6 to 12).

As an initial matter, applicants respectfully wish to point out to the Examiner that, contrary to the Examiner's assertion, there is presently evidence of record demonstrating the superior properties of the 40 kDa PEGylated IGFBP-4. It is not merely attorney arguments that have been presented. Data demonstrating the unexpected superiority of the 40 kDa PEGylated IGFBP-4 over unPEGylated and 20 kDa PEGylated IGFBP-4 is set forth as follows:

As shown in Fig. 3 of the application, wild type IGFBP-4 and the PEGylated forms of BP-4 have almost identical activity in cell culture assays. Therefore, the claimed modifications do not have a significant effect on the binding and inhibition of IGF.

Fig. 2 shows that the half life of PEGylated molecules is significantly prolonged in vivo. Modification with 20 kDa PEG shows significantly improved serum half life and serum levels in comparison to wild type IGFBP-4. PEGylation with 40 kDa PEG results

in dramatically and persistently higher serum levels and longer serum half life than observed for 20 kDa-PEG-IGFBP-4.

The improved serum kinetics of the claimed 40 kDa-PEG-IGFBP-4 results in significantly more potent inhibition of tumor growth than observed for the protein modified with 20 kDa PEG, as shown in example 14. Administration of 20 kDa-PEG-IGFBP-4 completely ***FAILED*** to inhibit tumor growth, but administration of 40 kDa-PEG-IGFBP-4 caused mean tumor volume to be reduced from 287 mm3 to 163 mm3. Additionally, two tumor markers were significantly reduced by treatment with 40 kDa-PEG-IGFBP-4 but not by treatment with 20 kDa-PEG-IGFBP-4.

Furthermore, as described in example 15, significant histopathological alterations of kidney tissue was induced by 20 kDa-PEG-IGFBP-4. These alterations were not observed for 40 kDa-PEG-IGFBP-4.

To the extent the Examiner asserts that these advantages are not recited in the claims, it is respectfully submitted that this is not required. "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

Thus, none of the cited references discloses or suggests that an IGFBP-4 PEGylated with a branched PEG residues of about 40 kDa has the superior properties relative to 20 kDa PEGylated IGFBP-4 as reported in the examples of the present application, and in particular none of the cited references provide any expectation that a 40kDa PEGylated IGFBP-4 would be less toxic than a conjugate with a 20 kDa PEG residue, as is demonstrated by the data in the present application.

The Examiner also acknowledges that there are "…multiple different species of PEG polymer…" available to those of ordinary skill in the art. None of the cited references points to the use of a PEG polymer that would result in the claimed compound, as the PEG reagent of Veronese is an amine-specific reagent, while the claimed compounds are PEGylated at cysteines. Following the teachings of Veronese, one might have tried to attach branched 40 kDa PEG to a free amino group of IGFBP-4, but would have had no reason to attempt to attach at cysteines, and would have absolutely no reason to expect that the resulting claimed molecule would have the

superior properties that it possesses. None of the cited art discloses a branched 40 kDa PEG reagent suitable for coupling to free thiols, as would be required to achieve the compound of the claims.

In light of the above arguments and amendments, it is respectfully submitted that the newly submitted claims are in condition for allowance, and such action is earnestly solicited.

No further fee is required in connection with the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

/David E. Wildman/

Attorney for Applicant(s)
David E. Wildman
(Reg. No. 40226)
340 Kingsland Street
Nutley, NJ 07110
Telephone (973) 235-6385
Telefax: (973) 235-2363

437092